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Pulmonary manifestations of anti-ARS antibody positive interstitial pneumonia — With or without PM/DM

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KEYWORDS
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Summary
Background: Autoantibodies against aminoacyl-tRNA synthetases (ARS) have been found to be highly specific for polymyositis and dermatomyositis (PM/DM) and to correlate strongly with complicating interstitial pneumonia (IP). The aim of the present study was to compare the clinical presentations of anti-ARS antibody-positive IP patients with or without manifestations of PM/DM.
Methods: We retrospectively examined 36 IP patients with anti-ARS antibodies. Sixteen patients presented with and 20 without the features of PM/DM. They were divided into PM/DM-IP and idiopathic-IP (IIP) groups. Clinical symptoms, findings on physical examination, laboratory data, pulmonary function, computed tomography (CT), and bronchoalveolar lavage fluid (BALF) cell counts were compared.
Results: Skin findings, myalgia, and elevation of serum creatinine kinase were found in the PM/DM-IP group. Features common to both groups included: volume loss in lower bilateral lobes; ground-glass opacities, reticular shadows and traction bronchiectasis on chest CT; high percentage of lymphocytes (IIP: 44.0% ± 21.0% (mean ± SD), PM/DM-IP: 50.5% ± 23.5%) and low CD4/8 ratios (IIP: 0.36 ± 0.34, PM/DM-IP: 0.44 ± 0.42) in BALF; decreased pulmonary function, including percentage of predicted vital capacity (VC) (IIP: 80.1% ± 15.4%, PM/DM-IP: 73.6% ± 16.4%), residual volume (RV) (IIP: 70.7% ± 21.7%, PM/DM-IP: 71.5% ± 17.1%), total lung

Abbreviations: anti-ARS antibodies, autoantibodies against aminoacyl-tRNA synthetases; PM/DM, polymyositis and dermatomyositis; IIP, idiopathic interstitial pneumonia; fNSIP, fibrotic nonspecific interstitial pneumonia.

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capacity (TLC) (IIP: 73.4% ± 13.6%, PM/DM-IP: 71.6% ± 13.0%), and diffusing capacity DLco (IIP: 57.5% ± 26.7%, PM/DM-IP: 46.4% ± 10.3%). Both groups achieved good responses to initial corticosteroid or immunosuppressant therapy.
Conclusion: Patients with anti-ARS antibody-positive IP have common pulmonary manifestations regardless of the presence of PM/DM.

Background

Autoantibodies against aminoacyl-tRNA synthetases (ARS), a group of cytoplasmic enzymes, have been found to be highly specific for polymyositis and dermatomyositis (PM/DM), and to strongly correlate with complicating interstitial pneumonia (IP). Eight anti-ARS autoantibodies have been identified. These include anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS, anti-Zo, and anti-Ha.[1–3]

Patients with anti-ARS antibodies often present with the following features: myositis, IP, inflammatory arthritis, Raynaud's phenomenon, mechanic's hands, and fever. These features and symptoms have been termed the "antisynthetase syndrome". However, some cases of IP with anti-ARS-antibody have no symptoms of myositis. Yoshimizu et al. have reported that there are common clinical and pathological findings and computed tomography (CT) findings in patients with interstitial lung disease and anti-ARS antibodies.[4] We conducted a retrospective, observational study to compare the clinical features of anti-ARS antibody-positive patients with either idiopathic IP (IIP) or with PM/DM-associated IP (PM/DM-IP).

Patients and methods

We identified 36 anti-ARS-antibody-positive patients with IP at Kanazawa University Hospital and our related facilities from January 2005 to December 2010. The patients in the present study are all Japanese. Anti-ARS antibody analysis was performed at the Department of Dermatology in Kanazawa University Hospital by immunoprecipitation using ^{35}S-methionine-labeled extracts of K562 cells.

The patients were divided into 2 groups, those with and without the features of PM/DM. There were 16 patients with the features of PM/DM, and their IP was designated as PM/DM-IP. The remaining 20 patients did not have any features of collagen vascular diseases, and their IP was designated as IIP. There were 14 women and 6 men in the IIP group (mean ± SD age at onset was 59.1 ± 13.0 years; range, 21–72 years), and 12 women and 4 men in the PM/DM-IP group (mean ± SD age at onset was 58.5 ± 7.9 years; range, 43–69 years). One woman in the PM/DM-IP group also had systemic scleroderma. We extracted and evaluated the following from the patients' medical records: clinical symptoms, physical examination, laboratory data, pulmonary function tests, CT findings, and bronchoalveolar lavage fluid (BALF) cell counts. Two pulmonologist (at least) and one radiologist examined the chest CT scan. Bronchoalveolar lavage was performed with 50 ml of saline for 3 times at the same site where bronchoscope was wedged. We analyzed cell differentiation of the third fraction by counting at least 300 cells on a smear prepared with a cytospin and Wright–Giemsa staining. Skin symptoms such as eruptions, nailfold bleeding, Gottron papules, mechanic's hands, and heliotrope rash were diagnosed by dermatologists specializing in collagen vascular diseases.

Statistical analysis

Variables are expressed as the mean ± SD unless otherwise stated. To detect differences between groups, Student's *t*-test was used for parametric data and the χ^2 square test was employed for categorical data. Analyses were performed using a statistical software package (StatView; SAS Institute Inc; Cary, NC). A *P*-value <0.05 was considered to be statistically significant.

Results

The types of anti-ARS antibodies detected are shown in Table 1. Anti-Jo-1 antibody was detected in 10 patients (27.8%), anti-KS in 3 patients (8.3%), anti-OJ in 2 patients (5.5%), anti-PL-12 in 4 patients (11.1%), anti-PL-7 in 4 patients (11.1%), and anti-EJ in 13 patients (36.1%).

Table 2A shows the clinical symptoms of each patient group. Nonproductive cough and dyspnea on exertion were frequently seen in both groups. Fever was noticed in 3 (16%) IIP patients and 7 (47%) PM/DM-IP patients ($P < 0.05$). Myalgia was seen in 7 (47%) PM/DM-IP patients but was not seen in the IIP patients ($P < 0.05$). Arthralgia was seen in 1 (5%) IIP patient and 3 (20%) PM/DM-IP patients. Raynaud's phenomenon was seen in 4 (21%) IIP patients and 2 (13%) PM/DM-IP patients. Fever and myalgia were more frequently investigated in the PM/DM-IP group than in the IIP group ($P < 0.05$).

Table 2B summarizes the findings on physical examination. Erythema and heliotrope were seen only in the PM/

Table 1 Types of anti-ARS antibodies.

	IIP	PM/DM-IP	Total (%)
Jo-1	4	6	10 (27.8)
KS	2	1	3 (8.3)
OJ	2	0	2 (5.5)
PL-12	4	0	4 (11.1)
PL-7	3	1	4 (11.1)
EJ	5	8	13 (36.1)
Total	20	16	36

IIP group; women $n = 14$, men $n = 6$, (median age 63 yrs, range 21–72 yrs) PM/DM group; women $n = 12$, men $n = 4$, (median age 60.5 yrs, range 43–69 yrs).

Table 2A Clinical symptoms.

	IIP (n = 19)		PM/DM-IP (n = 15)	
	Number	(%)	Number	(%)
Fever	3	(16)	7	(47)[a]
Dry cough	14	(74)	9	(60)
Dyspnea	13	(68)	10	(67)
Myalgia	0	(0)	7	(47)[a]
Altheralgia	1	(5)	3	(20)
Raynaud	4	(21)	2	13

[a] p Value <0.05 (by χ^2 square test).

DM-IP group. Nailfold bleeding was seen in 7 (43.8%) PM/DM-IP patients and 2 (11%) IIP patients. Gottron papules were seen in 5 (31.3%) PM/DM-IP patients and 1 (5%) IIP patient. Mechanic's hands were detected in 2 (11%) IIP patients and 5 (31.3%) PM/DM-IP patients.

Inspiratory fine crackles on auscultation of the chest were heard in every patient, but no patient had clubbed fingers. Erythema, nailfold bleeding, and Gottron papules were significantly ($P < 0.05$) more frequent in the PM/DM-IP group than in the IIP group.

Table 2C shows the CT findings. Lower lobe and peripheral predominant shadows, reticular shadows, ground-glass opacities, and traction bronchiectasis were seen in almost all the patients of both groups. Peribronchovascular candle shadows were detected in more than half of the cases of both groups. Honeycombing was seen only in the 1 patient with scleroderma. One patient in each group had mediastinal lymph node swelling.

Common features of chest CT were seen in both groups. We classified the CT findings in patients with IP as fibrotic nonspecific interstitial pneumonia (fNSIP) patterns except for 1 patient with definite honeycombing, whose findings were classified as an interstitial pneumonia fibrosis (IPF) pattern.

Table 3A shows the results of laboratory examinations at diagnosis. Data (Tables 3A–3C) are expressed as mean ± standard deviation. The serum KL-6, SP-D, SP-A, the white blood cell count (WBC) and the serum CRP levels of both groups were elevated, and the room-air PaO_2 was slightly decreased and A-aDO_2 was increased in both groups (PaO_2: 76.3 ± 12.1 and 77.9 ± 13.3 Torr; A-aDO_2: 21.5 ± 11.0 and 23.1 ± 13.9 Torr; respectively, for IIP and PM/DM-IP), which were not significantly different. These values tended to be elevated in the PM/DM-IP group, but there were no significant differences between the 2 groups. The serum creatinine kinase was significantly ($P < 0.05$) elevated in the PM/DM-IP group at 1350 ± 2238 IU/l vs. 87.7 ± 40.1 IU/l in the IIP group.

Table 3B shows the results of pulmonary function testing. Vital capacity (VC), expressed as percentage of the predicted value, was at the lower limit for normal for both groups, and residual volume (RV), total lung capacity (TLC) and lung carbon monoxide diffusing capacity DLco were decreased in both groups. No obstructive ventilatory

Table 2B Physical examinations.

	IIP (n = 19)		PM/DM-IP (n = 16)	
	Number	(%)	Number	(%)
Erythema	0	(0)	11	(68.8)[a]
Nailfold bleeding	2	(11)	7	(43.8)[a]
Gottron papules	1	(5)	5	(31.3)[a]
Heliotrope	0	(0)	2	(12.5)
Clubbed finger	0	(0)	0	(0)
Fine crackles	19	(100)	16	(100)
Mechanic's hand	2	(11)	5	(31.3)

[a] p Value <0.05 (by χ^2 square test).

Table 2C Chest CT findings.

	IIP (n = 18)		PM/DM-IP (n = 13)	
	Number	(%)	Number	(%)
LL-predominant	18	(100)	13	(100)
Peripheral-predominant	15	(83)	12	(92.3)
Reticular shadows	18	(100)	13	(100)
GGO	17	(94)	12	(92.3)
Consolidation	9	(50)	4	(30.7)
Peri-BVB shadows	12	(67)	11	(84.6)
Traction bronchiectasis	17	(94)	11	(84.6)
Honeycomb	1	(6)	0	(0)
Mediastinal LN swellings	1	(6)	1	(7.6)

Table 3A Laboratory data (mean ± SD).

	IIP (n = 20)	PM/DM-IP (n = 16)
KL-6 (U/ml)	1342 ± 794.6	1956 ± 2395
SP-D (ng/ml)	226.2 ± 41.7	245.4 ± 193.0
SP-A (ng/ml)	81.2 ± 41.7	86.8 ± 60.7
WBC ($\times 10^3$ μl)	8364 ± 3910	10264 ± 3243
CRP (mg/dl)	0.7 ± 0.7	1.58 ± 2.0
CK (IU/l)	87.7 ± 40.1	1350 ± 2238[a]
PaO2 (Torr)	76.3 ± 12.1	77.9 ± 13.3
A-aDO2 (Torr)	21.5 ± 11.0	23.1 ± 13.9

[a] p Value <0.05.

Table 3B Pulmonary function tests.

	IIP (n = 20)	PM/DM-IP (n = 16)
VC (% pred.)	80.1 ± 15.4	73.6 ± 16.4
FEV1/FVC (%)	78.7 ± 20.2	77.1 ± 14.6
RV (% pred.)	70.7 ± 21.7	71.5 ± 17.1
TLC (%)	73.4 ± 13.6	71.6 ± 13.0
RV/TLC (%)	33.8 ± 9.1	34.7 ± 6.0
DLco (% pred.)	57.5 ± 26.7	46.4 ± 10.3
DLco/VA (% pred.)	88.4 ± 25.3	77.2 ± 12.8

% pred.: predicted percentage.

Table 3C Bronchoalveolar lavage fluid cell counts.

	IIP ($n = 15$)	PM/DM-IP ($n = 13$)
TCC ($\times 10^5/\mu L$)	3.4 ± 1.7	3.4 ± 2.0
Macro (%)	44.8 ± 21.0	36.3 ± 25.0
Lym (%)	44.0 ± 22.6	50.5 ± 23.5
Neu (%)	8.6 ± 10.0	8.9 ± 6.3
Eo (%)	2.2 ± 5.6	4.4 ± 4.3
CD4/8	0.36 ± 0.34	0.44 ± 0.42

TCC: total cell count, Mac: macrophage, Lym: lymphocyte, Neu: neutrophil, Eo: eosinophil.

disorders were seen in either group. The values for DLco/alveolar volume (VA) were almost normal. There were no significant differences in the values for pulmonary function.

Table 3C shows results of BALF differential cell counts. BAL was undertaken in 17 IIP cases and in 13 PM/DM-IP cases. Two IIP cases were excluded from analysis because BAL was undertaken after the initiation of steroid treatment. High percentages of lymphocytes and low CD4/8 ratios were seen. These values were not significantly different.

Fig. 1 shows representative chest CTs from patients with each type of anti-ARS antibody. Every chest CT showed bilateral ground-glass opacities, linear and reticular shadows in the lower lobes, predominantly subpleural. Shadow characteristics were similar regardless of the type of anti-ARS antibody detected in the patient.

Table 4 summarizes the treatments. Prednisolone (PSL) treatment was started as the primary treatment in almost all cases, and was effective in almost all cases at the initiation of treatment. In some cases, however, lung fibrosis worsened and immunosuppressant drugs were added while PSL was tapered. In one PM/DM-IP patient who had anti-Jo-1 antibody, PSL treatment was very effective, and treatment could be completed and PSL could be stopped. In another PM/DM-IP case with anti-EJ antibody, who was treated with a pulse of methylprednisolone (mPSL-p) and a pulse of cyclophosphamide (CY-p), her IP rapidly worsened and she died despite intensive therapy. One patient had concomitant lung cancer, and died without initiation of corticosteroid therapy.

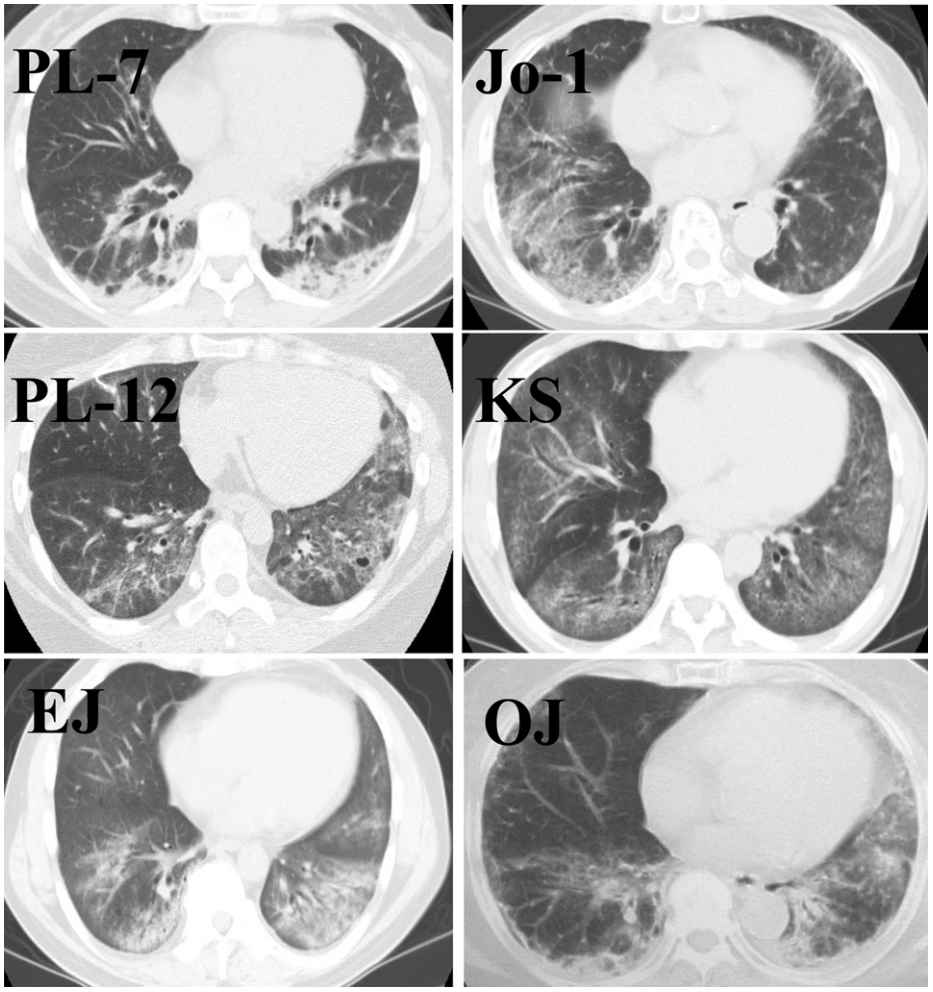

Figure 1 Representative chest computed tomography (CT) findings for patients with different anti-ARS antibodies. Every chest CT demonstrates bilateral ground-glass opacities and linear and reticular shadows in the lower lobes, predominantly subpleural.

Table 4 Treatment.

	PSL only	PSL + CYA (or TAC)	mPSL-p + PSL	mPSL-p + PSL + CYA	CY pulse + PSL + CYA	None	mPSL-p + CY pulse	Total
IIP	11	2	1	2	1	3	0	20
PM/DM-IP	8	4	1	1	1	0	1	16

PSL: prednisolone, mPSL-p: methylprednisolone pulse.
CYA: cyclosporin, CY: cyclophosphamide, TAC: tacrolimus.

Discussion

Interstitial pneumonia (IP) is a common and serious complication of PM/DM, particularly in patients with anti-ARS antibody. Anti-ARS antibodies are found in approximately 25%—35% of patients with PM/DM. Anti-Jo-1 antibody is the most frequent antibody identified in PM/DM (15%—20%), followed by anti-PL-7 and anti-PL-12 (5%—10%).[3] In our study, patients with anti-EJ were the most frequent, followed by patients with anti-Jo-1. The clinical features of our patients were remarkably similar in patients with anti-ARS antibody-positive IP, with or without PM/DM. It is thought that pulmonary manifestations such as IP may precede PM/DM symptoms if anti-ARS antibodies are detected. Kalluri et al. reported that IP with PL-12 antibody preceded manifestations of connective tissue disease in sixteen out of thirty-one patients (53%).[5] There is a report of a patient with pulmonary fibrosis in whom anti-Jo-1 antibody preceded the diagnosis of PM diagnosis by 12 months.[6] Patients with IP and anti-ARS antibodies but without myositis have been noted since the 1980s.[7—10] There was a previous report that 5 of 10 patients positive for anti-ARS antibody without evidence of myositis were responsive to therapy.[11]

We expected that elevated serum CK levels and symptoms such as erythema and myalgia would predominate in the PM/DM group. But in this study, some patients in the IIP group also had fever and nail-fold bleeding, although most patients in that group did not have any apparent PM/DM symptoms. We found that many patients achieved good responses to prednisolone or immunosuppressive therapy. All patient's CK levels are normal in IIP group. Seven of 16 patient's CK levels are increased in PM/DM-IP group. They are decreased and normalized after treatment in all these seven cases. Skin findings were diagnosed and followed regularly by dermatologist at Kanazawa University Hospital. Some patients transferred, we can follow 16 of 20 patients in IIP group (five cases of 16 have skin lesions), 15 of 16 patients (twelve case of the 15 have skin lesions) in DM/PM-IP group. The skin lesions are improved in all cases after treatment. However, some patients recurred following dose reduction. Patients with anti-ARS antibodies have chronic and mild IP[4]; however, some patients have acute progressive respiratory failure.[11] One woman with anti-PL-12-antibody-positive IIP had scleroderma. The IP might have been associated with scleroderma, and she was the only case with honeycombing. She did not meet the criteria of PM/DM.

It was reported that patients with anti-ARS antibody-positive IP have common clinical and pathological features.[4] In that study, 14 patients with anti-ARS antibodies were examined. They concluded their results indicated that patients with ILD usually have a good response to corticosteroid treatment, however some have a rapidly worsening course and recurrence, despite therapy. They had nonspecific interstitial pneumonia (NSIP) and/or organizing pneumonia (OP) patterns on chest CT, increase lymphocyte in BALF in 7 of 11 patients, which are similar to our findings. There were no significant differences in pulmonary manifestations between the patients with IIP and PM/DM-IP. In some patients, their IP worsened or their muscles weakened when they were tapered off steroids, which suggests that we need to observe patients carefully with regard to the appearance of PM/DM symptoms during follow-up.

Conclusions

There were no significant differences in the pulmonary manifestations of IP in patients with anti-ARS antibody, whether or not PM/DM was evident. Patients with chronic IP, especially with NSIP findings on CT, should be tested for anti-ARS antibodies. Detection of antibodies is important for estimating their clinical course.

Conflict of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

None of authors have any financial and personal relationships with other people or organizations that could inappropriately influence.

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